

## **REMARKS**

Claims 32-56 are currently pending in the Application. Of these claims, Claims 35, 37, and 38 stand withdrawn from consideration in view of a prior species election.

The newly added claims 57-82 are consistent with previously elected Group I, comprising claims relating to miRNA, and read upon the elected species of claims covering the use of polymerase chain reaction. Support for the amplifying signal, as recited in new Claim 60, is found, *e.g.*, at page 28, lines 3-7, and page 29, lines 3-5. Support for new Claims 81 and 82, comprising a second unlabeled probe, is found throughout the specification, *e.g.*, as diagrammed schematically in Figures 2 and 4, and as described, *e.g.*, at page 4, lines 8-13.

The Examiner has raised a number of objections and rejections. For clarity, these objections and rejections are listed below in the order in which they will be addressed:

1. The application allegedly fails to comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures;
2. The Abstract is objected to for allegedly referring to the merits of the invention;
3. Claim 32 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite;
4. Claims 32, 33, 48-52, and 54 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,607,834 to Bagwell, *et al.*, (hereinafter "Bagwell") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau");
5. Claims 32, 33, 36, and 39-55 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,866,336 to Nazarenko (hereinafter "Nazarenko") in view of Lau;
6. Claim 34 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bagwell in view of Lau, in further view of U.S. Patent No. 5,985,557 to Prudent, *et al.*, (hereinafter "Prudent");
7. Claim 34 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nazarenko in view of Lau, in further view of Prudent;
8. Claim 56 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bagwell in view of Lau, in further view of U.S. Patent No. 5,985, 563 to Hyidig-Nielsin, *et al.*, (hereinafter "Hyidig-Nielsin");

9. Claim 56 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nazarenko in view of Lau, in further view of Hyidig-Nielsin.

### **Objections**

1. The Examiner alleges that the application fails to comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, the Examiner asserts that Figures 12, 26, and 27 comprise sequences that do not have sequence identifiers. With respect to Figures 26 and 27, as the present application does not contain Figures 26 and 27, Applicant believes that the Examiner intended to indicate Figures 24 and 25, which are sheets 26 and 27 out of 27 drawing sheets.

Applicants respectfully point out that the sequences appearing in Figures 12, 24 and 25 are included in the Sequence Listing filed in paper copy on August 23, 2004, and in a substitute Computer Readable Form on November 16, 2004. The CRF was filed along with a Certification that the paper and CRF copies are the same. Further, in a Preliminary Amendment and Response to Notice of Missing Parts filed on August 23, 2004, the specification was amended so that the brief descriptions of Figures 12, 24 and 25 contain the sequence identifiers for the nucleic acid sequences shown in these figures, in accordance M.P.E.P. §2429 instructions for compliance with 37 CFR 1.821(b) with respect to sequences appearing in drawings. As such, Applicants submit that the application complies with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures and respectfully request that these objections be removed.

2. The Abstract is objected to for allegedly referring to the merits of the invention. The Examiner specifically objects to the use of the word "improved." While not acquiescing to the Examiner's arguments, Applicants herein amend the Abstract text to remove the word "improved," and respectfully request that this objection be removed.

### **REJECTIONS**

#### **The Claims Are Not Indefinite**

3. Claim 32 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. In particular, the Examiner asserts that the phrase "wherein said second region can form a hairpin loop when said probe is hybridized" is unclear as to whether the

One of skill in the art would appreciate that a limitation describing a region that "can form a hairpin" when the probe is hybridized to a target nucleic acid indicates that a) the probe contains portions that are complementary to each other, and b) the complementary portions are not precluded from hybridizing to each other when the probe is hybridized to the target nucleic acid. Applicants submit that this element is clear, for the reasons recited above. Nonetheless, for business reasons and without acquiescing to the Examiner's argument, and reserving the right to prosecute the original or a similar claim in one or more future applications, Applicants herein amend Claim 32 to recite "wherein said unlabeled probe comprises a first region that is complementary to said microRNA and a second region that is not complementary to said microRNA, wherein "a first portion of said second region is complementary to a second portion of said second region, wherein said first portion and said second portion can hybridize to each other when said unlabeled probe is hybridized to said microRNA." Applicants submit that Claim 32 is not indefinite and respectfully request that this rejection be removed.

### **The Claims Are Not Obvious**

Prima facie obviousness requires 1) a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings; 2) the prior art must teach of a reasonable expectation of success should the suggested combination or modification take place; and 3) the prior art must teach or suggest all the claim limitations. M.P.E.P § 2143. A showing of obviousness will fail if any one of these elements is not met. As explained in more detail below, none of the cited combinations of references cited sets forth each and every element of the rejected claims.

4. Claims 32, 33, 48-52, and 54 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bagwell in view of Lau (Office Action page 5). Claims 33, 48-52, and 54 depend from Claim 32 and incorporate each recited element of Claim 32. Claim 32 as amended recites contacting a microRNA with an unlabeled probe to form an RNA detection structure. New Claim 57 and dependent claims further recite detection of the RNA detection structure using an amplification reaction.

As the Examiner has noted, Bagwell does not disclose microRNA detection (Office Action page 5). Bagwell is directed toward probes comprising fluorescent labels and teaches nucleic acid detection using a probe comprising a minimum of two

fluorophore (see, e.g., col 5, line 20). The teachings of Bagwell are, in fact, antithetical to the concept of using of an unlabeled probe. Lacking teachings of either microRNA detection or the use of unlabeled probes for such detection, Bagwell clearly does not disclose an RNA detection structure comprising a microRNA and an unlabeled probe. Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or the formation of an RNA detection structure comprising a microRNA and an unlabeled probe. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Bagwell and Lau does not teach or suggest all the limitations of Claims 32, 33, 48-52, and 54, or newly added claims 57-82, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

**5.** Claims 32, 33, 36, and 39-55 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nazarenko in view of Lau (Office Action page 6). Claim 32 as amended recites contacting a microRNA with an unlabeled probe to form an RNA detection structure. New Claim 57 and dependent claims further recite detection of the RNA detection structure using an amplification reaction.

As the Examiner has noted, Nazarenko does not disclose microRNA detection (Office Action page 7). Nazarenko teaches nucleic acid detection using oligonucleotides labeled a donor and acceptor pair for "molecular energy transfer" ("MET", e.g., fluorescence resonance energy transfer, or "FRET") (See, e.g., col 15, lines 18-20). As with Bagwell, the teachings of Nazarenko are, in fact, antithetical to the concept of using of an unlabeled probe. Lacking teachings of either microRNA detection or the use of unlabeled probes for such detection, Nazarenko clearly does not disclose an RNA detection structure comprising a microRNA and an unlabeled probe. Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or the formation of an RNA detection structure comprising a microRNA and an unlabeled probe. While Applicants do not acquiesce that the other elements necessary for establishing prima facie

obviousness have been met, Applicants submit that the combination of Nazarenko and Lau does not teach or suggest all the limitations of Claims 32, 33, 36, and 39-55, or newly added claims 57-82, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

6. Claim 34 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bagwell in view of Lau, in further view of Prudent (Office Action page 9). Claim 34 depends from Claim 32 and incorporates each recited element of Claim 32. Claim 32 as amended recites contacting a microRNA with an unlabeled probe to form an RNA detection structure. New Claim 57 and dependent claims further recite detection of the RNA detection structure using an amplification reaction.

As the Examiner has noted, Bagwell does not disclose microRNA detection (Office Action page 5). Bagwell teaches nucleic acid detection using a probe comprising a minimum of two fluorophores (see, e.g., col 5, line 20). As noted above, the teachings of Bagwell are, in fact, antithetical to the concept of using of an unlabeled probe. Lacking teachings of either microRNA detection or the use of unlabeled probes for such detection, Bagwell clearly does not disclose an RNA detection structure comprising a microRNA and an unlabeled probe. Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or the formation of an RNA detection structure comprising a microRNA and an unlabeled probe. The further combination with Prudent fails to cure the deficiencies of Bagwell and Lau. Prudent does not teach an RNA detection structure comprising a microRNA and an unlabeled probe. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Bagwell, Lau, and Prudent does not teach or suggest all the limitations of Claim 34, or newly added claims 57-82, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

7. Claim 34 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nazarenko in view of Lau, in further view of Prudent (Office Action page 10). Claim 34

depends from Claim 32 and incorporates each recited element of Claim 32. Claim 32 as amended recites contacting a microRNA with an unlabeled probe to form an RNA detection structure. New Claim 57 and dependent claims further recite detection of the RNA detection structure using an amplification reaction.

As the Examiner has noted, Nazarenko does not disclose microRNA detection (Office Action page 7). Nazarenko teaches nucleic acid detection using oligonucleotides labeled a donor and acceptor pair for "molecular energy transfer" ("MET", e.g., fluorescence resonance energy transfer, or "FRET") (See, e.g., col 15, lines 18-20). As noted above, the teachings of Nazarenko are, in fact, antithetical to the concept of using of an unlabeled probe. Lacking teachings of either microRNA detection or the use of unlabeled probes for such detection, Nazarenko clearly does not disclose an RNA detection structure comprising a microRNA and an unlabeled probe. Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or the formation of an RNA detection structure comprising a microRNA and an unlabeled probe. The further combination with Prudent fails to cure the deficiencies of Nazarenko and Lau. Prudent does not teach an RNA detection structure comprising a microRNA and an unlabeled probe.

While Applicants do not acquiesce that the other elements necessary for establishing *prima facie* obviousness have been met, Applicants submit that the combination of Bagwell, Lau, and Prudent does not teach or suggest all the limitations of Claim 34, or newly added claims 57-82, and the cited art therefore fails to establish *prima facie* obviousness. Applicants respectfully request that this rejection be removed.

8. Claim 56 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bagwell in view of Lau, in further view of Hyidig-Nielsin (Office Action page 11-12). Claim 56 depends from Claim 32 and incorporates each recited element of Claim 32. Claim 32 as amended recites contacting a microRNA with an unlabeled probe to form an RNA detection structure. New Claim 57 and dependent claims further recite detection of the RNA detection structure using an amplification reaction.

As the Examiner has noted, Bagwell does not disclose microRNA detection (Office Action page 5). Bagwell teaches nucleic acid detection using a probe comprising a minimum of two fluorophores (see, e.g., col 5, line 20). As noted above, the teachings of Bagwell are, in fact, antithetical to the concept of using of an unlabeled probe. Lacking teachings of either microRNA detection or the use of unlabeled probes for such detection, Bagwell clearly does not disclose an RNA detection structure comprising a microRNA and an unlabeled probe. Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or the formation of an RNA detection structure comprising a microRNA and an unlabeled probe. The further combination with Hyidig-Nielsin fails to cure the deficiencies of Bagwell and Lau. Hyidig-Nielsin teaches methods of detecting sexually transmitted diseases using PNA probes. Hyidig-Nielsin does not teach an RNA detection structure comprising a microRNA and an unlabeled probe. While Applicants do not acquiesce that the other elements necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Bagwell, Lau, and Hyidig-Nielsin does not teach or suggest all the limitations of Claim 56, or newly added claims 57-82, and the cited art therefore fails to establish prima facie obviousness. Applicants respectfully request that this rejection be removed.

9. Claim 56 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Nazarenko in view of Lau, in further view of Hyidig-Nielsin (Office Action page 13). Claim 56 depends from Claim 32 and incorporates each recited element of Claim 32. Claim 32 as amended recites contacting a microRNA with an unlabeled probe to form an RNA detection structure. New Claim 57 and dependent claims further recite detection of the RNA detection structure using an amplification reaction.

As the Examiner has noted, Nazarenko does not disclose microRNA detection (Office Action page 5). Nazarenko teaches nucleic acid detection using a probe comprising a minimum of two fluorophores (see, e.g., col 5, line 20). As noted above, the teachings of Nazarenko are, in fact, antithetical to the concept of using of an unlabeled probe. Lacking teachings of either microRNA detection or the use of unlabeled probes for such detection, Nazarenko clearly does not disclose an RNA detection

structure comprising a microRNA and an unlabeled probe. Lau fails to cure this deficiency. Lau teaches the observation of microRNAs in *C. elegans*. However, Lau fails to teach the use of unlabeled probes in the detection of microRNA, or the formation of an RNA detection structure comprising a microRNA and an unlabeled probe. The further combination with Hyidig-Nielsin fails to cure the deficiencies of Nazarenko and Lau. Hyidig-Nielsin teaches methods of detecting sexually transmitted diseases using PNA probes. Hyidig-Nielsin does not teach an RNA detection structure comprising a microRNA and an unlabeled probe. While Applicants do not acquiesce that the other elements necessary for establishing *prima facie* obviousness have been met, Applicants submit that the combination of Nazarenko, Lau, and Hyidig-Nielsin does not teach or suggest all the limitations of Claim 56, or newly added claims 57-82, and the cited art therefore fails to establish *prima facie* obviousness. Applicants respectfully request that this rejection be removed.

## **CONCLUSION**

For the reasons set forth above, it is respectfully submitted that all rejections have been addressed and should be removed, and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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